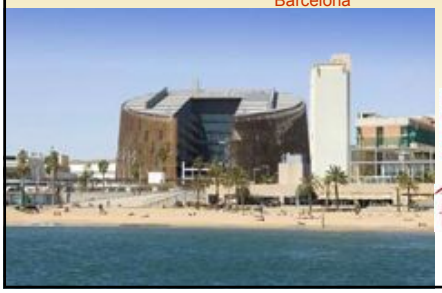
What will we know when we will have the complete sequence of each of our genomes?

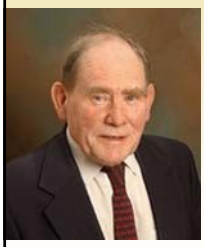
Jaume Bertranpetit
Universitat Pompeu Fabra
Barcelona



INSTITUT de BIOLOGIA EVOLUTIVA
CSIC UPF

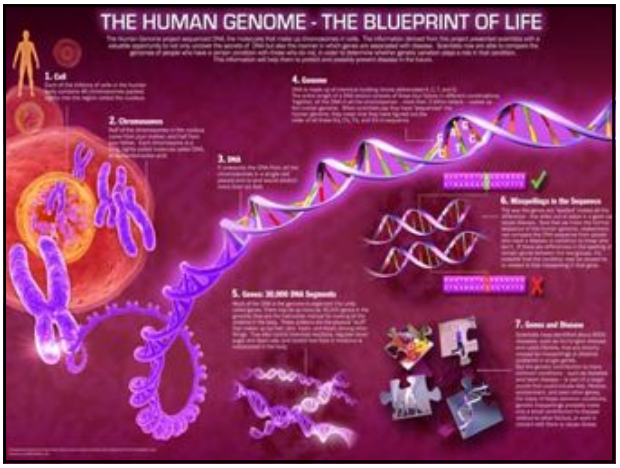
UNIVERSITAT POMPEU FABRA

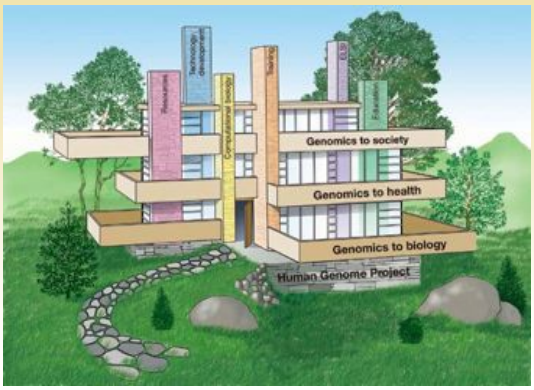
The revolution in the Life Sciences



Living organisms may be viewed as the only part of the natural world whose members contain internal description of themselves.
This is why the whole biology must be rooted in the DNA, and our task is still to discover how these DNA sequences arose in evolution and how they are interpreted in to build the diversity of the living world, including disease.

Sydney Brenner, dec 2012, Science





Forms of genomic variation

Sequence

- **Single base-pair changes** – point mutations (**SNPs**, Single Nucleotide Polymorphisms: 3Mb diff between any two genomes)
- **Small insertions/deletions**
- **Variable number of tandem repeats (microsatellite, minisatellite**
- **Mobile elements**—retroelement insertions (300bp -10 kb in size)
- **Large-scale genomic variation** (>10 kb)
  - Large-scale Deletions and Amplifications
  - Segmental Duplications / Copy Number Variation (**CNVs**, Up to 15Mb diff. between any two genomes)
- **Chromosomal variation**—translocations, inversions, fusions.

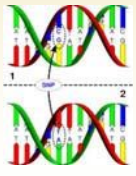
Cytogenetics

Forms of genomic variation

SNPs in the Human Genome

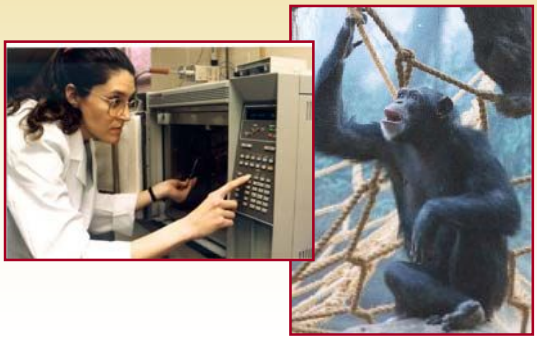
- Normally biallelic (two variants)
- Allelic frequencies present differences between populations.
- Phenotypic effect: normally without effect

- Public databases for SNPs
http://www.nhgri.nih.gov,
http://www.snp.cshl.org



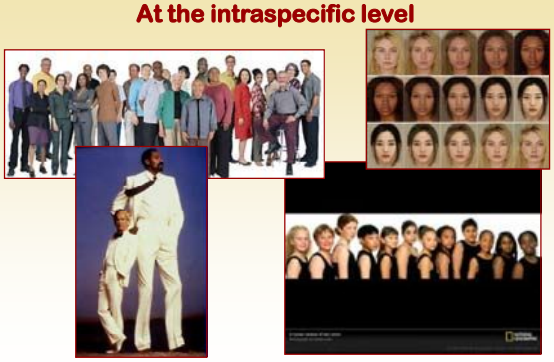
Linking genes and phenotypes

At the interspecific level



Linking genes and phenotypes

At the intraspecific level



Linking genomic and phenotypic variation

GENOTYPE VARIATION

↓

Genetic Epidemiology, Statistical Genomics, Systems Biology...

↓

PHENOTYPE (Disease) VARIATION

Disease as a phenotype

Types of disease:

Molecular classification of human diseases

Exogenous diseases: Infections, Intoxication, Nutritional *(NURTURE)*

Genetic diseases:
- Cell? Germinal or somatic
- Alteration? - Genic (mutations, ins/del) - Chromosomal
- Genome? -Nuclear -Mitocondrial

↓

Simple pattern of inheritance *(NATURE)*

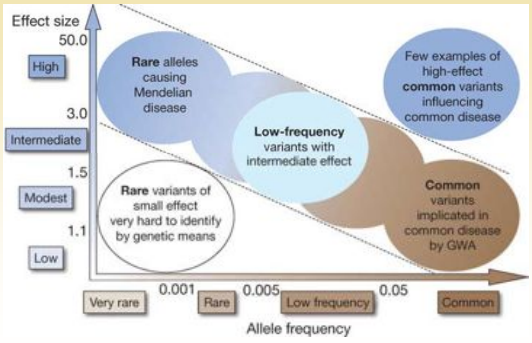
Complex or multifactorial diseases: *(NATURE vs NURTURE)*

Disease as a phenotype

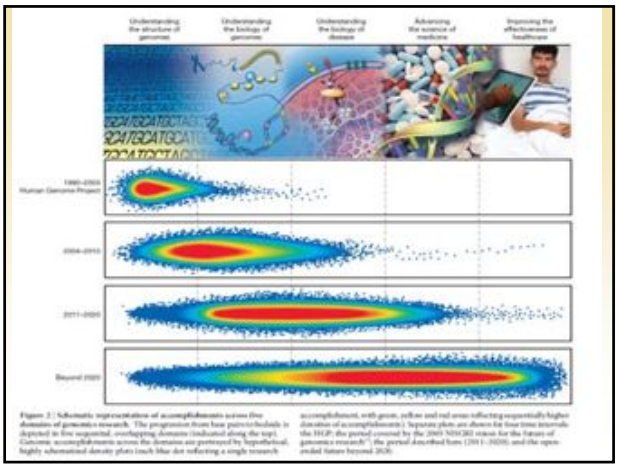
✓Complex diseases

- High prevalence
  - -Cardiopathy
  - -Reumatoid Arthritis
  - -Aunoimmune disease
  - -Psichiatic diseases
  - -Cancer
- Relevant genetic component
- No simple mendelian inheritance pattern
- Several genes with small contrintion (susceptibility)
- Multiple alleles interacting among themselves and with the environment.

Allele frequency and genetic effect

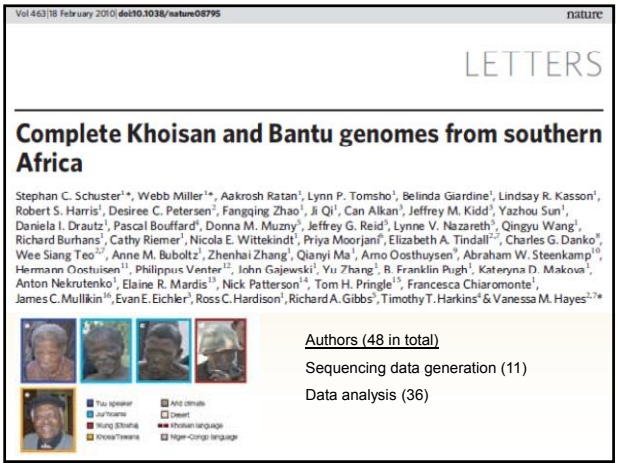


From: TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature08494



Sequencing of individual genomes

Genome	Journal/Source	Year
J. Craig Venter	PLoS Biology	2007
James D. Watson	Nature	2008
Marjolein Kriek	LUMC	2008
Yoruban African	Nature	2008
Han Chinese	Nature	2008
Stephen Quake	Nature Biotechnology	2009
George Church	Personal Genome Project	2009
Hermann Hauser	Illumina	2009
2 Koreans	Nature/Genome Research	2009
9 individuals	Knome	2009
Desmond Tutu	Nature	2010
!Gubi	Nature	2010
186 individuals	1000 Genomes Project	2010


Vol 463|18 February 2010|doi:10.1038/nature08795 nature

LETTERS

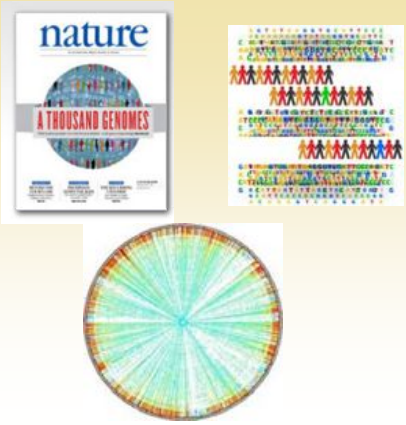
Complete Khoisan and Bantu genomes from southern Africa

Stephan C. Schuster[1]*, Webb Miller[1]*, Aakrosh Ratan[1], Lynn P. Tomsho[1], Belinda Giardine[1], Lindsay R. Kasson[1], Robert S. Harris[1], Desiree C. Petersen[2], Fangqing Zhao[1], Ji Qi[1], Can Alkan[3], Jeffrey M. Kidd[3], Yazhou Sun[1], Daniela I. Drautz[1], Pascal Bouffard[4], Donna M. Muzny[5], Jeffrey G. Reid[5], Lynne V. Nazareth[5], Qingyu Wang[1], Richard Burhans[1], Cathy Riemer[1], Nicola E. Wittekindt[1], Priya Moorjani[6], Elizabeth A. Tindall[2,7], Charles G. Danko[6], Wee Siang Teo[2,7], Anne M. Buboltz[1], Zhenhai Zhang[1], Qianyi Ma[1], Arno Oosthuysen[9], Abraham W. Steenkamp[10], Hermann Oostuisen[11], Philippus Venter[12], John Gajewski[1], Yu Zhang[1], B. Franklin Pugh[1], Kateryna D. Makova[1], Anton Nekrutenko[1], Elaine R. Mardis[13], Nick Patterson[14], Tom H. Pringle[15], Francesca Chiaromonte[1], James C. Mullikin[16], Evan E. Eichler[3], Ross C. Hardison[1], Richard A. Gibbs[5], Timothy T. Harkins[4] & Vanessa M. Hayes[2,7]*

Authors (48 in total)

Sequencing data generation (11)

Data analysis (36)



Deep resequencing in human populations

Resequencing of 200 human exomes identifies an excess of low-frequency non-synonymous coding variants **Li *et al.* 2010**

Deep resequencing reveals excess rare recent variants consistent with explosive population growth **Coventry *et al.* 2010**

Demographic history and rare allele sharing among human populations **Gravel *et al.* 2011**

Recent Explosive Human Population Growth Has Resulted in an Excess of Rare Genetic Variants **Keinan *et al.* 2012**

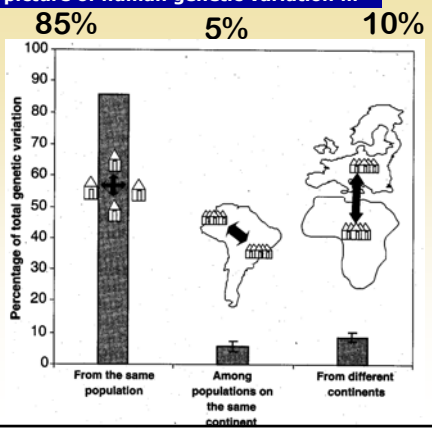
Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes **Tennessen *et al.* 2012**

An Abundance of Rare Functional Variants in 202 Drug Target Genes Sequenced in 14,002 People **Nelson *et al.* 2012**

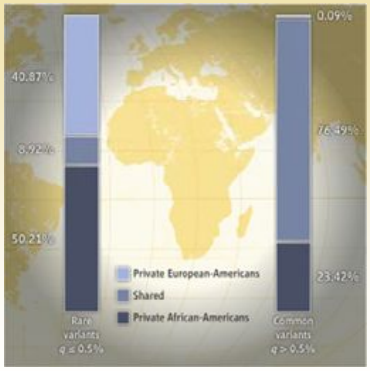
rare is meaningful

human populations show an excess of rare variants, which are enriched for disease causing mutations

The old picture of human genetic variation ...



... and the new picture



From Casals and Bertranpetit. *Science* 2012 . *Human Genetic Variation, Shared and Private.*

The case of my individual genome

1.- Color-blindness

2.- Disease risk (complex diseases)

3.- Carrier status (severe genetic diseases)

4.- Traits (physical characteristics)

5.- Drug response

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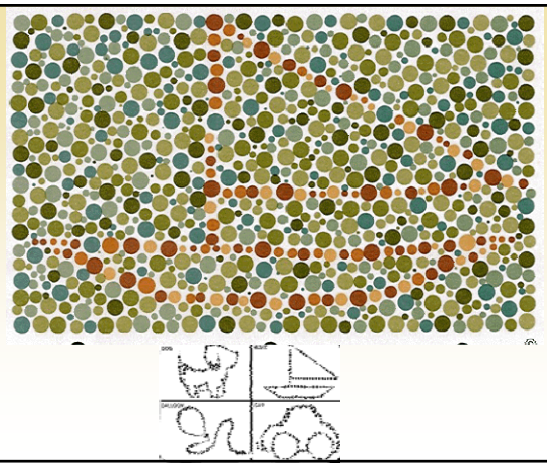

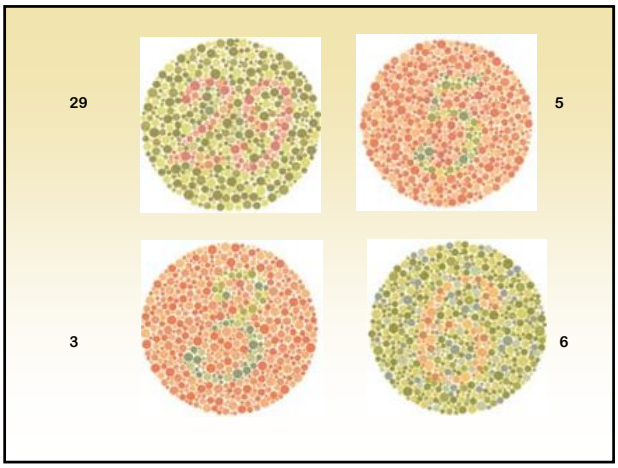
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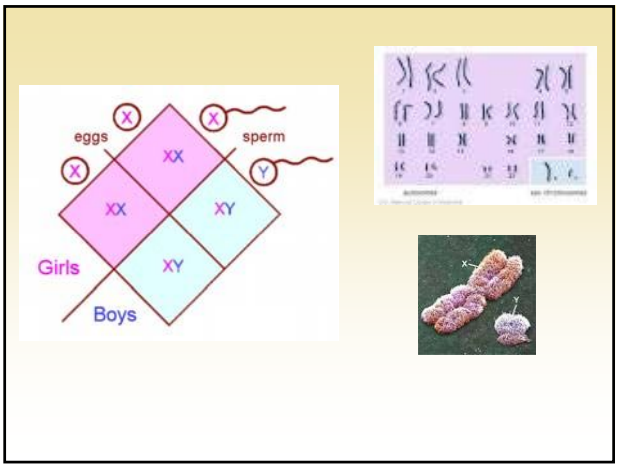
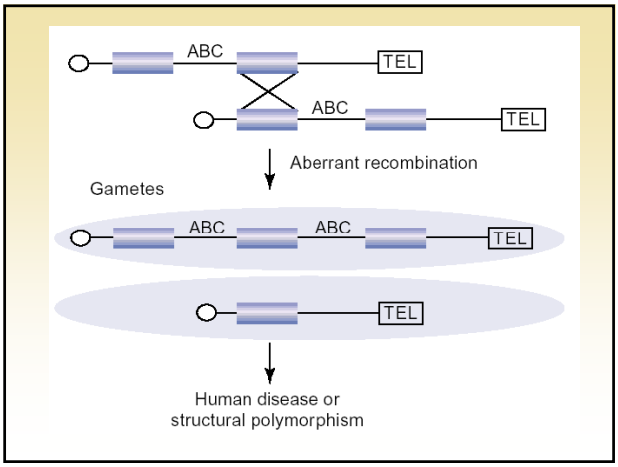

eggs
sperm
XX
XY
XX
XY
Girls
Boys


ABC
TEL
ABC
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Aberrant recombination
Gametes
ABC
ABC
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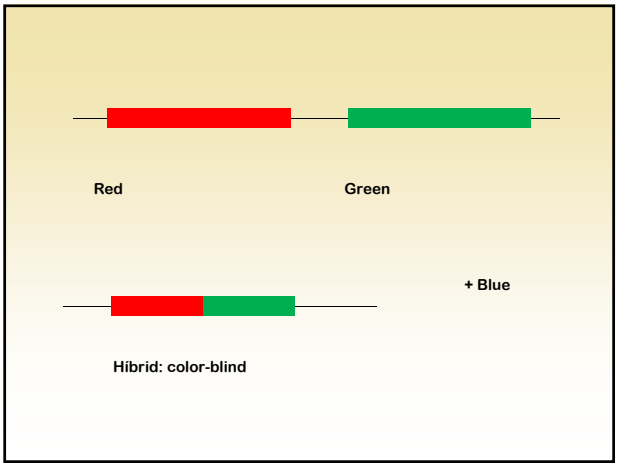
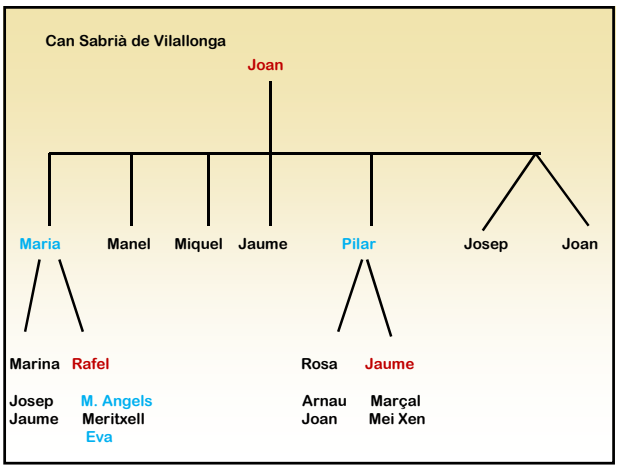
TEL
Human disease or
structural polymorphism


Red
Green
+ Blue
Híbrid: color-blind


Can Sabrià de Vilallonga
Joan
Maria
Manel
Miquel
Jaume
Pilar
Josep
Joan
Marina
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Rosa
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Josep
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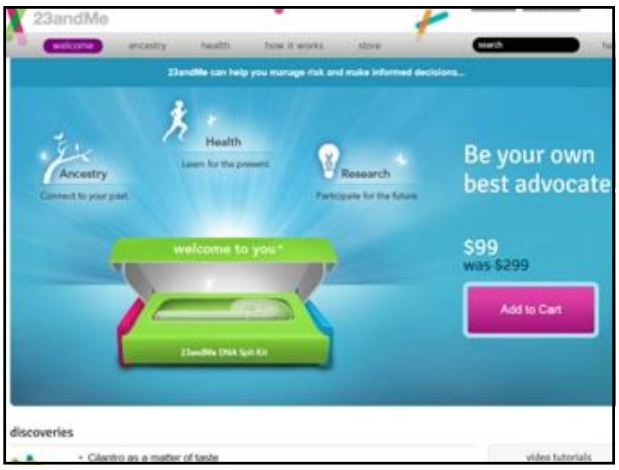
M. Angels
Meritxell
Eva
Arnau
Joan
Marçal
Mei Xen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was $299
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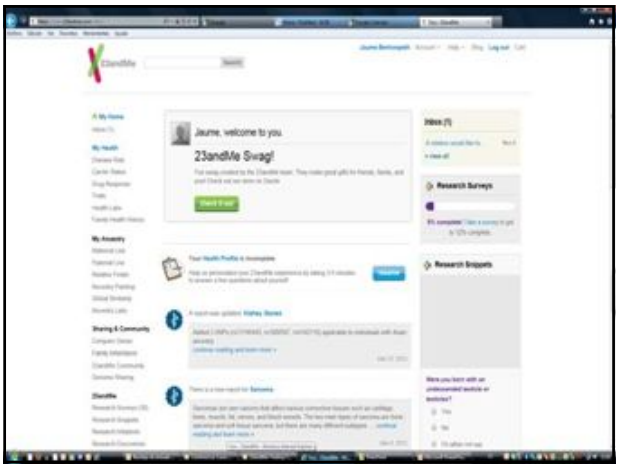
discoveries



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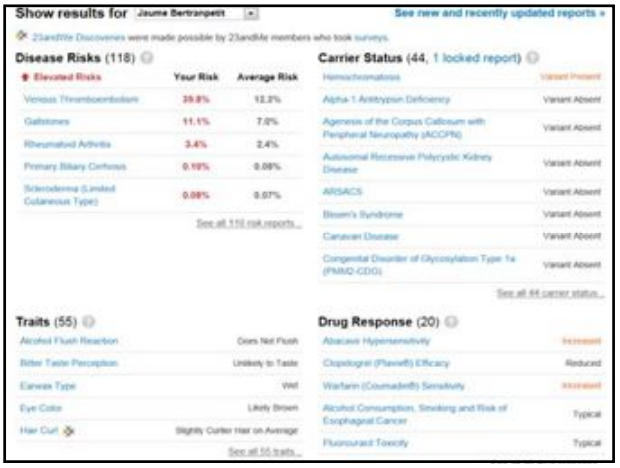

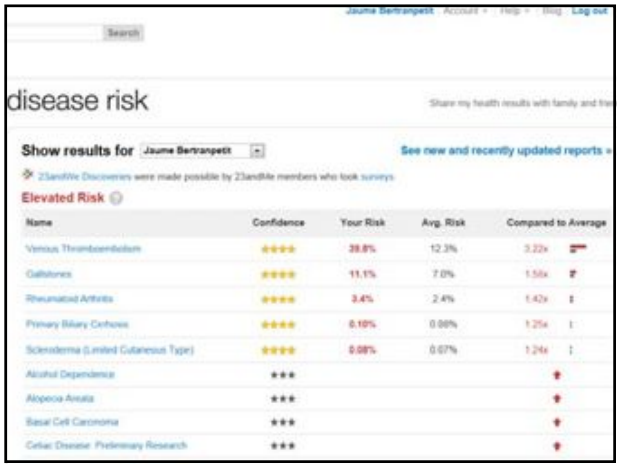

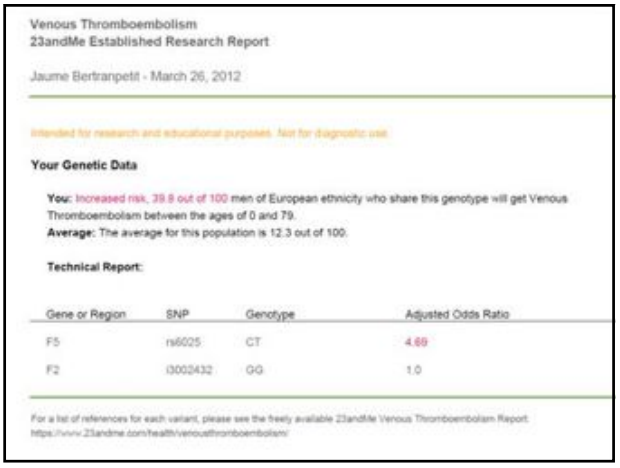

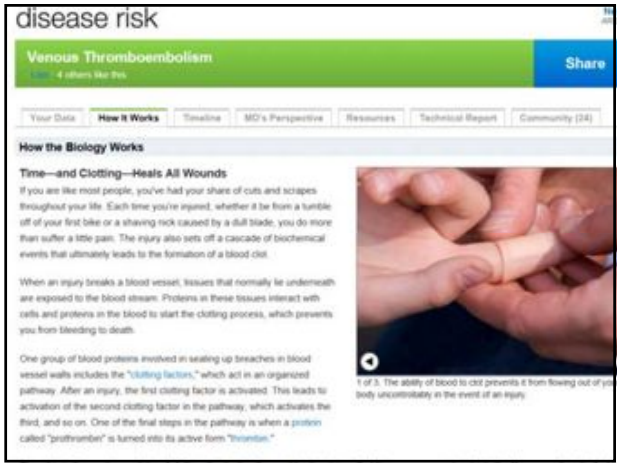

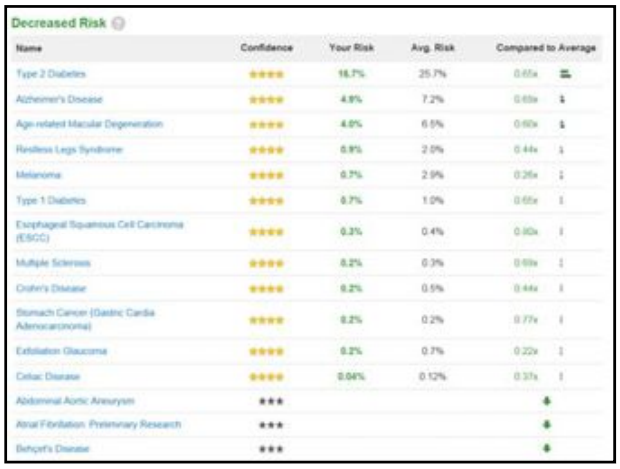

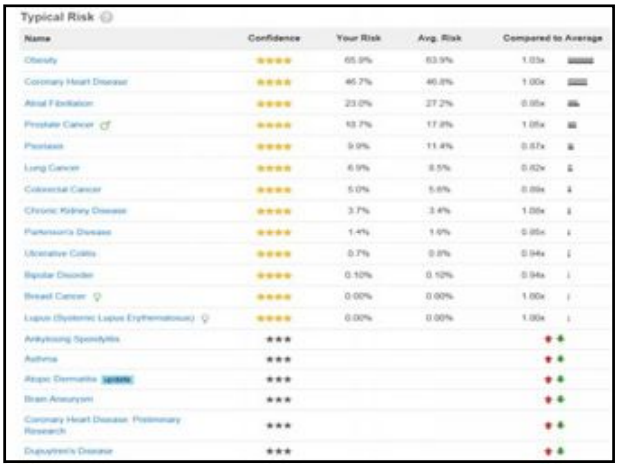

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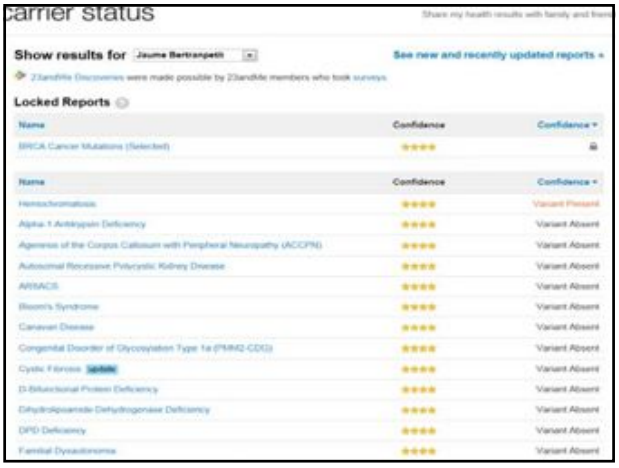

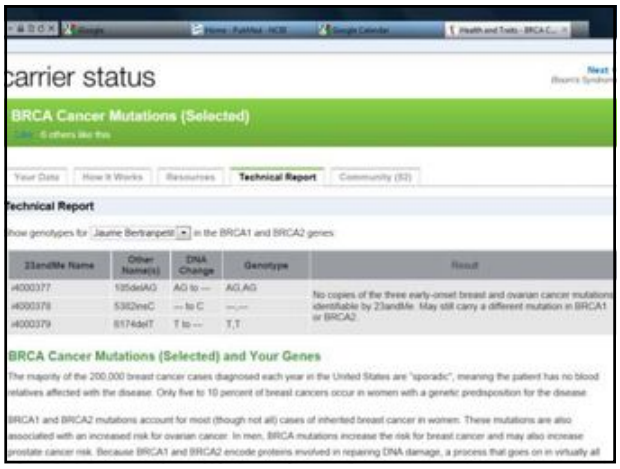

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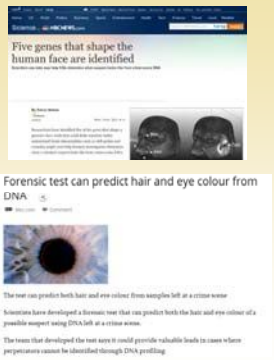

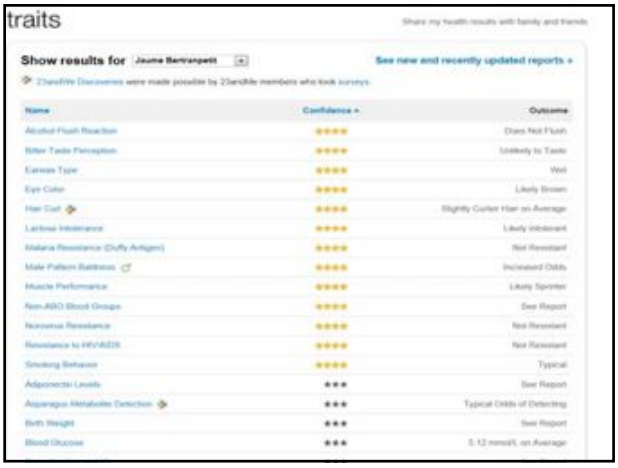

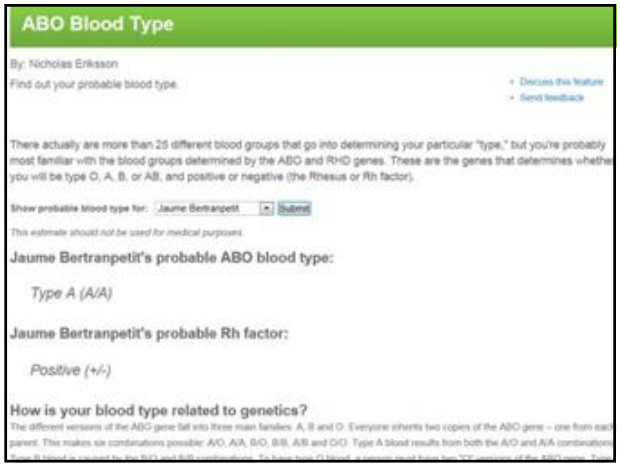

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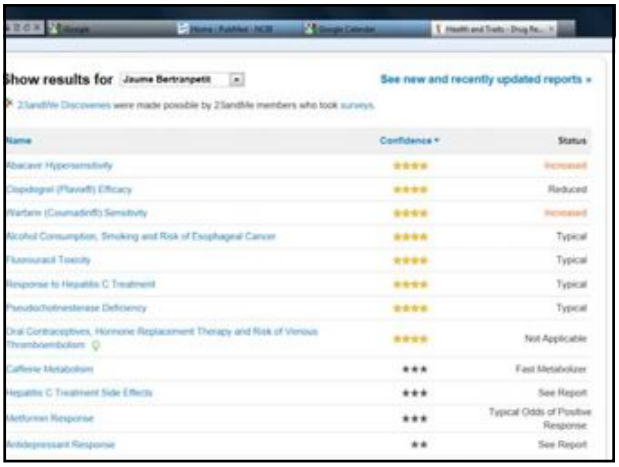

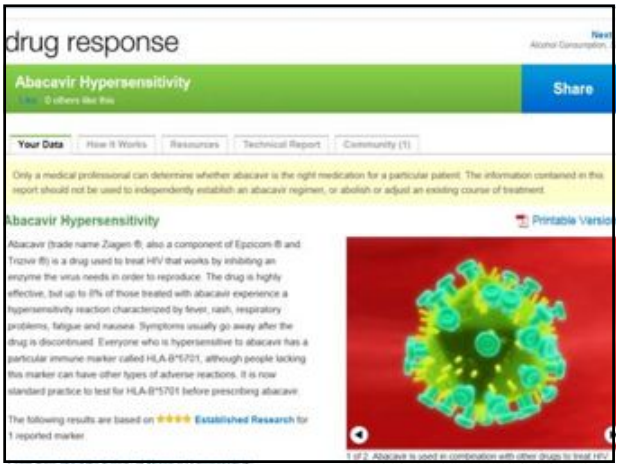

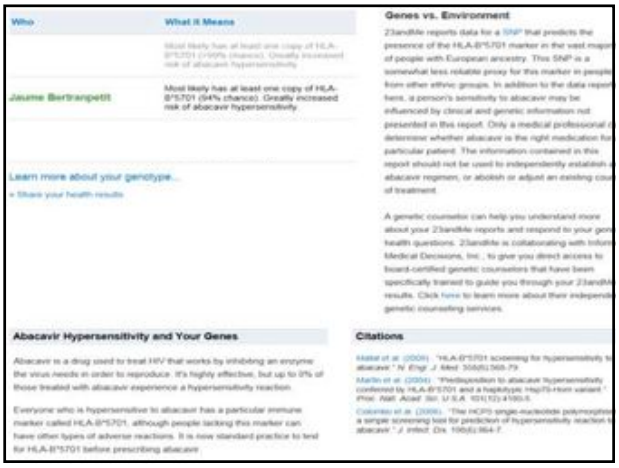

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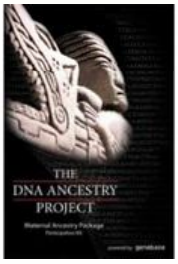
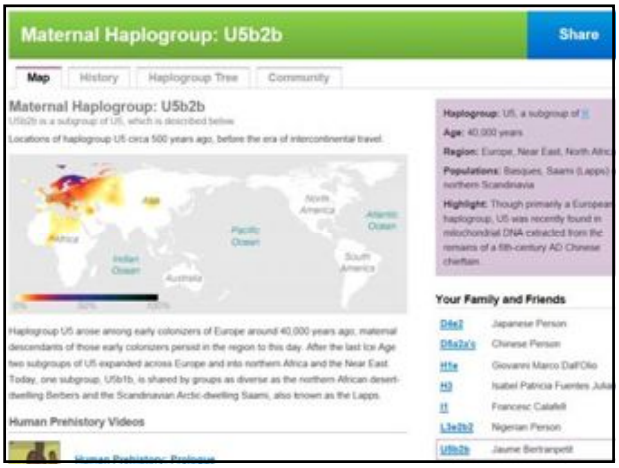
ancestryDNA™





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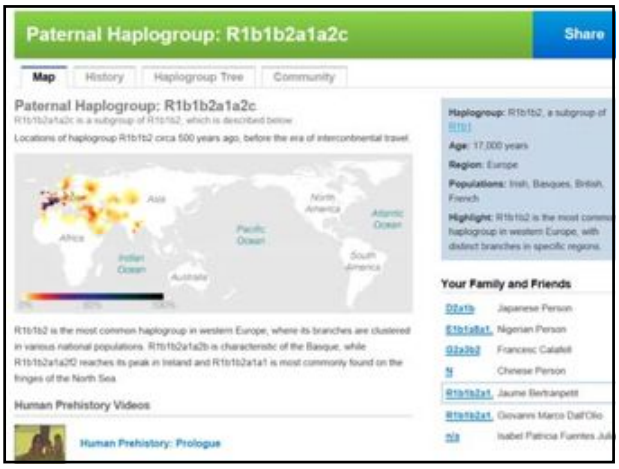
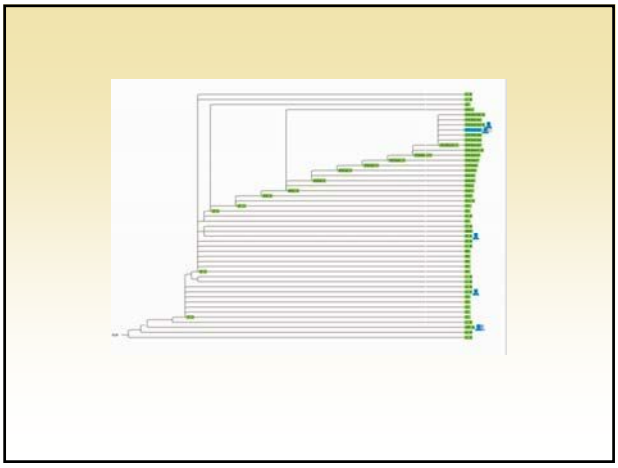
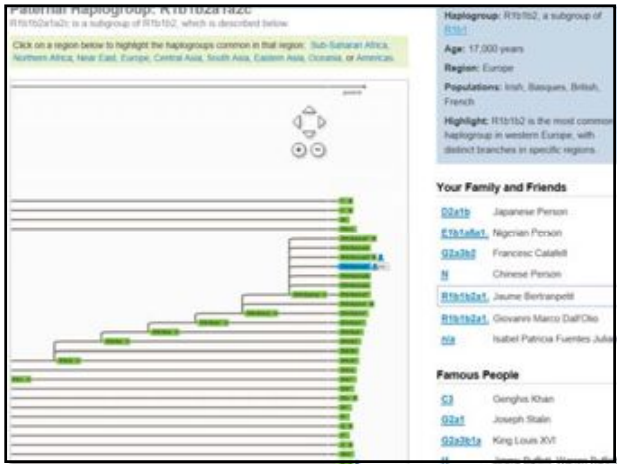






The case of my individual genome

1.- Color-blindness

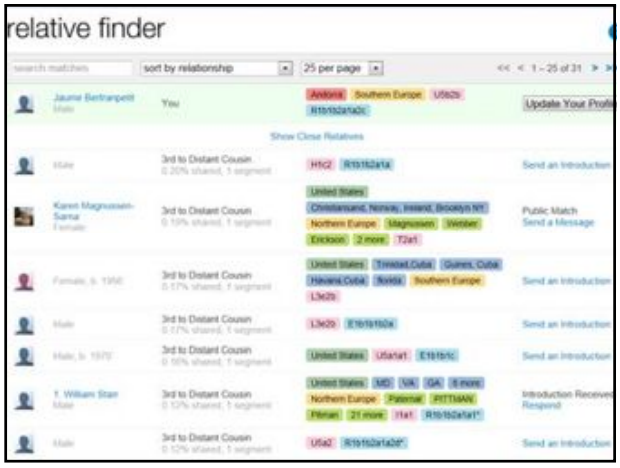
2.- Disease risk (complex diseases)

3.- Carrier status (severe genetic diseases)

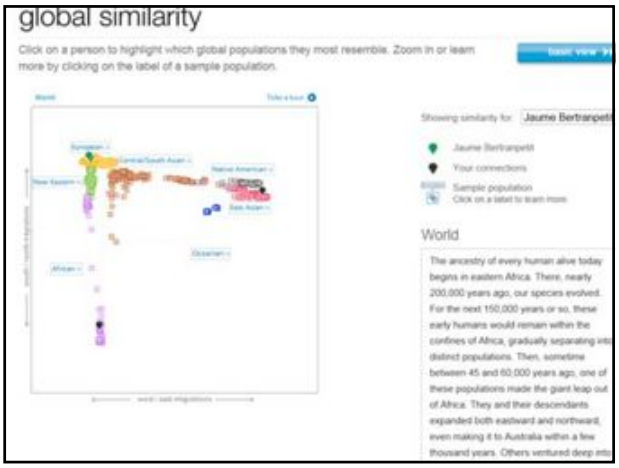
4.- Traits (physical characteristics)

5.- Drug response

6.- Ancestry (origins)
- Maternal origin (mtDNA)
- Paternal origin (Y-chromosome)
- **Autosomal genome**

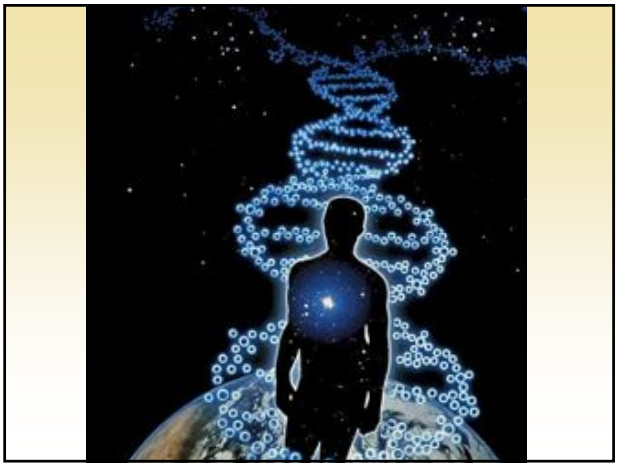


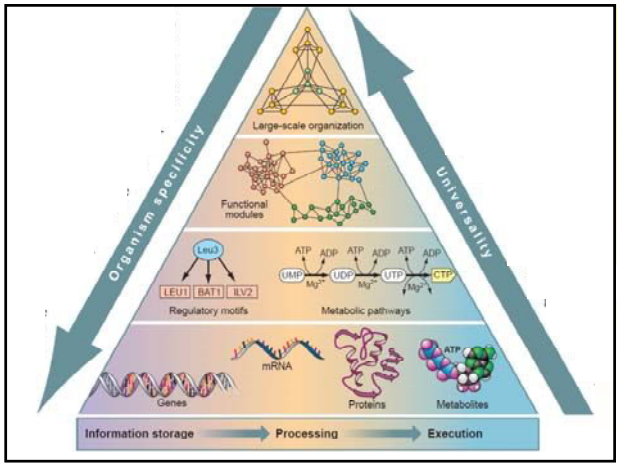

ancestry painting
Trace the ancestry of your chromosomes, one segment at a time. Last updated April 18, 2011.
Chromosome View
Solid segments indicate that both chromosomes come from the same geographic region. See a Cambodian Woman's painting
Dual-colored segments indicate chromosomes from different geographic regions. See an African American Man's painting
Gray segments indicate regions where 23andMe's genotyping chip has no markers
Select a person: Jaume Bertranpetit
Jaume Bertranpetit
Europe 100%
Asia 0%
Africa 0%
Worldwide Examples
Click on the icons in the map below to see example paintings of individuals from across the globe.


global similarity
Click on a person to highlight which global populations they most resemble. Zoom in or learn more by clicking on the label of a sample population.
Showing similarity for: Jaume Bertranpetit
Jaume Bertranpetit
Your connections
Sample population
Click on a label to learn more
World
The ancestry of every human alive today begins in eastern Africa. There, nearly 200,000 years ago, our species evolved. For the next 150,000 years or so, these early humans would remain within the confines of Africa, gradually separating into distinct populations. Then, sometime between 45 and 60,000 years ago, one of these populations made the giant leap out of Africa. They and their descendants expanded both eastward and northward, even making it to Australia within a few thousand years. Others ventured deep into


ancestry composition
36.0%


Neanderthal Ancestry
Share
Got Neanderthal DNA?
An estimated 2.6% of your DNA is from Neanderthals.
MODERN HUMANS
NEANDERTHALS
Friends & Family
You are ranked 3rd among your friends.




Organism specificity
Universality
Large-scale organization
Functional modules
Regulatory motifs
Metabolic pathways
mRNA
Genes
Proteins
Metabolites
Information storage
Processing
Execution